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Characterizing aggressiveness and predicting future progression of CF lung disease ☆

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Abstract

Cystic fibrosis (CF) is a life-shortening genetic disease characterized by variability in age of death that is largely due to variability in rate of progression of lung disease, the primary cause of mortality. Recognizing which individuals have more aggressive disease phenotypes and predicting their risk of immediate lung disease progression is a critical step in managing CF lung disease and extending the life expectancy of CF patients. Studies using observational CF patient registries have yielded useful methods for predicting future rate of disease progression and can be used to determine the impact that chronic pulmonary therapies have on slowing rate of lung function decline.

Keywords: Disease progression; Risk factors; Severity; Decline

1. Introduction

Cystic fibrosis (CF) is a common life-shortening, childhood onset inherited disorder that affects the lungs, pancreas and other organ systems [1]. Each year, approximately 1,000 persons in the United States receive a diagnosis of CF [2]. Although both the median age of death and expected median survival of persons with CF in the US have steadily increased, > 80% of premature deaths continue to result directly or indirectly from loss of lung function [3]. For this reason, spirometric measurements of lung function (particularly forced expiratory volume in 1 second; FEV_1) are important surrogate measures of disease progression and survival in CF.

Unfortunately, conventions around the use of FEV_1 (and more importantly, that fraction of FEV_1 retained relative to a "predicted" FEV_1 based on age, sex, and height: FEV_1 % predicted) to define CF lung disease can be confusing, and at times contradictory. For instance, it is common for age-independent grouping of patients by FEV_1 % predicted to be referred to as stratification by "disease severity", with labels of "severe, moderate, mild, and asymptomatic" assigned to different subgroups. In this context, "severity" is a cross-sectional term referring to the degree of pathologic deterioration of the lung, and might better be substituted with terms such as "condition" or "stage". Confusion arises because CF is a progressive, life shortening disease, and the severity should correlate with length of survival, with more rapid progression and earlier death identified as a more "severe" disease course. For example, a 10 year old and a 30 year old with CF and 40% of their predicted FEV_1 values are at the same *stage* of lung destruction, but it is clear that the severity of their respective disease courses has been different. The 30 year old has clearly experienced *slower* progression and has had a *milder* disease course than the 10 year old, even though they are currently at similar stages of lung disease. At some point earlier in life, the 10 year old was at an early stage of lung disease, but given the rapidity of lung disease progression, was "mild" ever an appropriate label for this child's CF lung disease?

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Confusion of disease stage with disease severity may be more than a simple semantic issue; epidemiologic data suggest that clinical intervention is much more intense in CF patients with advanced lung disease than at earlier stages [4]. Yet there are young CF patients with aggressive disease who are at high risk for rapid progression and who might benefit from more rigorous intervention at early stages. Does defining their lung disease severity as "mild" enable this process, or does it reinforce a "wait and see" attitude that these patients can hardly afford?

The aim of this paper is to clarify distinctions between CF lung disease stage and severity of affliction, and to suggest that recent insights into estimation of risk of future lung disease progression using patient risk factors can improve the rationale (and presumably the benefits) of therapeutic intervention in CF.

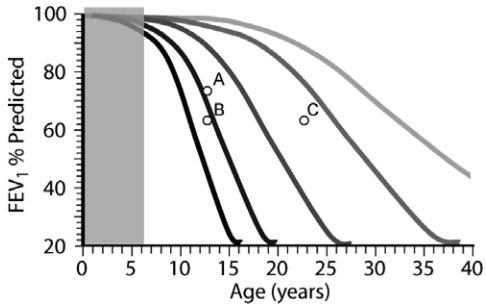

Fig. 2. Comparison of disease aggressiveness of different CF populations. A, B, and C represent three distinct CF populations. Populations A and B are the same age, but differ by 10% FEV_1 predicted. Populations B and C have the same FEV_1 % predicted, but differ in age by 10 years. Hypothetical disease course curves allow comparison of the relative disease aggressiveness associated with these populations.

2. Assessing disease severity using decline in FEV_1

The course of lung disease in persons with CF can be described by plotting their FEV_1 % predicted throughout their lifetime (Fig. 1). Although traditional spirometry cannot be reliably performed under the age of 6 years, we believe that lung function is essentially normal (i.e. at 100% of predicted value) for newborns with CF. As lung disease progresses with age, FEV_1 % predicted is lost, and the rate of disease progression at any given time is represented by the slope of this curve (as FEV_1 % predicted/year; Fig. 1A). Both prospective and retrospective analyses have suggested that the age at which this curve intersects with 20% predicted can predict age of death [5,6]. Fig. 1A is an idealized depiction of such a plot; Fig. 1B shows this idealized plot overlaid with actual cross-sectional data from all patients at a single CF center, demonstrating that there is a high degree of variability in progression of CF lung disease (i.e. that there is not a single disease course as in Fig. 1A, but rather that there are multiple possible courses, as in Fig. 1B).

Understanding this variable rate of progression is integral to appreciating the distinction between the aggressiveness of an individual's CF disease phenotype and the stage of their lung disease, and why an individual's FEV_1 % predicted alone is inadequate to characterize the aggressiveness of their disease. The idealized progression curves in Fig. 1B illustrate variability of disease phenotype. The earlier in time that a given curve intersects 20% FEV_1 predicted, the earlier the predicted age of death for patients following that curve, and thus the more aggressive their phenotype. This method of representation helps explain two epidemiologic observations. First, for two groups of CF patients of the same age but with a 10 point difference in FEV_1 % predicted (e.g. groups A and B of Fig. 2), the group with the lower FEV_1 (group B) has a two-fold lower 2-year survival compared to the other group. Second, for two groups of CF patients with the same FEV_1 % predicted but 10 years difference in age (e.g. groups B and C of Fig. 2), the *younger* group (group B) has a two-fold lower 2-year survival relative to the older group [7]. While it may seem obvious that group B has demonstrated a more aggressive disease phenotype than group A, it may not be obvious that group A has expressed a more aggressive phenotype than group C, even though group C is at a more advanced stage of disease. This is a situation where the historical precedent of referring to disease stage as

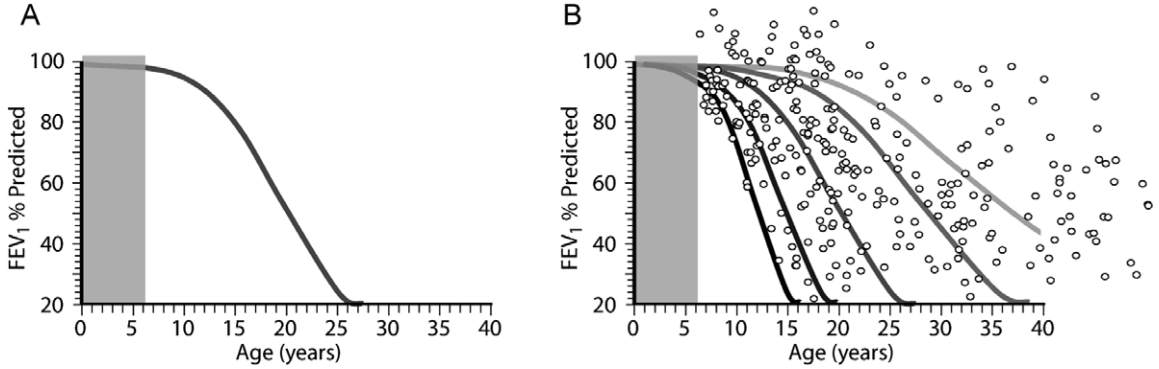

Fig. 1. Plotting FEV_1 % predicted versus age. Panel A: The disease course of a hypothetical CF patient. FEV_1 % predicted is not reliably collected before age 6 (gray box). At any given time, the curve slope is a measure of rate of lung function decline (as FEV_1 % predicted/yr). Estimation of when this curve will intersect with 20% FEV_1 predicted is a robust predictor of age of death (in this case, approximately 26 years). Panel B: Overlay of data for all patients from a single CF care center at a given time. Additional curves have been added to reflect the diversity of disease courses within this population. Curves that intersect with 20% predicted earlier in time represent populations with more aggressive disease courses and earlier mortality. Curves that intersect later in time represent less aggressive disease courses.

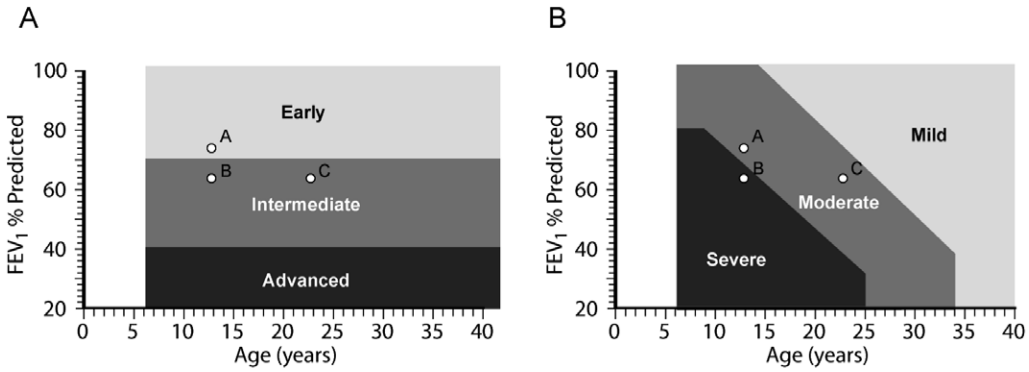

Fig. 3. Topography of disease stage and disease aggressiveness. Panel A: Division of the CF population into three lung disease stages (early, intermediate, and advanced) based upon FEV_1 % predicted. Populations A and B from Fig. 2 are at different stages, while populations B and C are at the same stage of disease. Panel B: Division of population based upon aggressiveness of lung disease. This topographical depiction is adapted from an analysis by Schluchter et al. [8] modeling the least and most aggressive CF disease course quartiles among ΔF508 homozygotes. Using this algorithm, population B from Fig. 2 has the most aggressive disease, and the aggressiveness of population A is likely greater than that of population C, even though population A is at an earlier disease stage.

"disease severity" can cause confusion, since groups B and C are at the same disease stage (Fig. 3A), but likely differ with respect to disease aggressiveness. A "topographical" depiction of CF lung disease aggressiveness as a function of FEV_1 % predicted and age as generated by Schluchter et al. [8] illustrates this point (Fig. 3B).

3. Risk factors that predict rate of FEV_1 decline

Although the age and the FEV_1 % predicted of an individual can help identify the relative aggressiveness of their CF phenotype, they do not necessarily provide a good prediction of the *risk* that an individual has for future rapid disease progression. In other words, they can tell you where a patient has come from, but not necessarily where they are going. Given that the goal of pulmonary interventions are ultimately to retard the disease process and thereby reduce the rate of lung function decline, the ability to predict future rate of decline is essential for making rational decisions regarding intervention.

A number of studies conducted at single treatment centers and/or with small numbers of patients have identified factors associated with an increased risk of future lung disease progression. These include, but are not limited to, young age, high lung function, female sex, certain CFTR genotypes and modifier genes, pancreatic insufficiency, poor nutritional status, lower socioeconomic status, respiratory viral infections, infection with *Pseudomonas aeruginosa* or *Burkholderia cepacia*, and diabetes mellitus. More recently, the Epidemiologic Study of Cystic Fibrosis (ESCF) [9], a multicenter, prospective encounter-based observational study of over 30,000 CF patients conducted in the US and Canada from 1994 to 2005, was used to assess these and other potential risk factors for FEV_1 decline in children and adolescents with CF. 4,923 patients aged 6–17 years were studied by repeated-measures mixed model regression to estimate mean rates of change of FEV_1 % predicted and the influence of potential risk factors identified in the previous year on observed rates. Patients were stratified into age groups of 6 to 8 years, 9 to 12 years, and 13 to 17 years, and studied over a mean observation period of 5.5 years [10].

Table 1
Risk factors for decline in FEV_1 for children and adolescents in any of the age groups 6 to 8 years, 9 to 12 years, and 13 to 17 years (adapted from Konstan et al. [10])

– Baseline FEV_1
– Gender
– *P. aeruginosa* in last sputum culture during the past year
– Weight-for-age percentile at last clinic visit during the past year
– Daily sputum production*
– Crackles *
– Wheezing *
– Sinusitis *
– Annual incidence of exacerbations treated with i.v. antibiotic
– Elevated liver function tests *
– Pancreatic enzyme use *

* Condition present during >50% of visits during the past year.

Of 28 potential risk factors investigated, 11 had a significant univariate association with rate of FEV_1 decline in any age group, and were retained in the final multiple regression analysis (Table 1). Overall rates of decline were −1.12, −2.39 and −2.34% predicted per year in 6–8-year-olds, 9–12-year-olds and 13–17-year-olds, respectively. Statistically significant risk factors for all age groups were high baseline FEV_1, sex, and the presence of crackles. In contrast, other previously recognized risk factors were only found to be statistically significant in two of the three age groups studied: *Pseudomonas* infection was not a significant risk factor in 13–17-year-olds, intravenous antibiotic treatment for pulmonary exacerbation was not a significant risk factor in 9–12-year-olds, and daily sputum production and low weight for age were not significant risk factors in 6–8-year-olds.

Using this more comprehensive analysis, it is now possible to predict the rate of an individual child or adolescent's lung function decline over the next 4 years based on his or her clinical history by adding the independent effect of each risk factor exhibited by the patient to the overall rate of decline for his or her age group [10]. For example, a 10-year-old

boy with pancreatic insufficiency, FEV_1 of 103% predicted, weight-for-age at the 20% percentile and a positive culture for *Pseudomonas*, but no other identified risk factors, can be predicted to lose 3.22% predicted FEV_1 per year, i.e. 13% predicted over the next 4 years.

Risk factors for poor future lung function in children under 6 years old were assessed in an earlier ESCF analysis in which FEV_1 at age 6 years was correlated with clinical characteristics exhibited at 3 years of age [11]. Low weight-for-age and height-for-age percentiles as well as the presence of crackles, *Pseudomonas* infection, daily sputum, cough and clubbing at age 3 were all associated with lower FEV_1 at 6 years of age.

4. Therapies associated with slowing decline in FEV_1

As mentioned earlier, the value of determining an individual's CF lung disease aggressiveness (independent of disease stage) and predicting their future risk of lung function decline is best realized when interventions known to retard rate of decline can be administered. Unfortunately, there are little data to demonstrate that most commonly used chronic CF pulmonary therapies impact rate of lung function decline. Because of variability in disease course and rate of decline over short time periods, randomized clinical trials have almost exclusively focused on 'sustained improvement' in lung function as the pulmonary outcome measure, which may or may not translate into slower decline. Prospective demonstration of a therapeutic impact on rate of lung function decline requires observation over periods of several years [12] and to date only one chronic CF therapy, high dose ibuprofen, has been prospectively shown to impact lung function decline [13,14].

The availability of large CF patient registries has made it possible to retrospectively test whether chronic pulmonary therapies have impacted CF lung function decline, although these analyses are complicated and not without significant limitations. Nevertheless, a retrospective analysis of high dose ibuprofen use, employing the CF Foundation Patient Registry, has demonstrated that such relationships can be detected [15]. Of the 6–17-year-old patients with FEV_1 >60% predicted who were in the Patient Registry between 1996 and 2000, 1,365 patients were treated with ibuprofen while 8,960 patients were not. The rate of decline in FEV_1 was compared in treated versus untreated patients using an analysis that adjusted for several risk factors [15]. Over an average observation period of 2–7 years, the mean annual rate of decline in FEV_1 % predicted was 27% slower in patients treated with ibuprofen (−1.48% predicted/yr) than in untreated patients (−2.08% predicted/yr).

The ESCF observational study is also being used to assess the effect of various therapies on lung function decline. The first reported analysis of this type evaluated the use of inhaled corticosteroids [16]. Chronic inhaled corticosteroids were used by 2,978 patients 6–17 years old. FEV_1 decline changed from −1.52 to −0.44% predicted per year after initiation of this therapy. In a second analysis of 2,230 patients 8–38 years old followed for at least 4 years, initiating dornase alfa was associated with a statistically significant reduction in the rate of decline in FEV_1 relative to a comparator group [17]. It is likely that other therapies will be similarly studied in the future. Such studies will provide important reassurance that chronic therapies, which can represent both additional treatment burden and cost to patients and caregivers, are capable of modifying CF lung disease progression.

5. Conclusions

FEV_1 % predicted is a surrogate for survival in CF patients that is used to identify the stage of CF lung disease progression. Traditionally CF lung disease stage has been termed "disease severity" with categories of "asymptomatic mild, moderate, or severe", but this terminology does not account for the effect of age in defining disease severity. The problem is most obvious when a child is at an early stage of a very aggressive lung disease course. Although at an early stage of lung disease, this child is unlikely to reach adulthood and there will never be anything "mild" about the severity of his or her affliction. If we contrast this hypothetical CF child with an adult male with near-normal lung function who has been recently diagnosed with CF due to infertility, their relative lung functions may be their only shared characteristic. To the extent that qualifiers such as "mild" or "severe" disease impact a clinician's willingness to intervene therapeutically, they are best reserved for describing the aggressiveness of disease phenotype.

The rate at which FEV_1 % predicted declines at any time in a patient's life is an important indicator of the aggressiveness of their CF lung disease, *independent* of their lung disease stage. The high variability of an individual's FEV_1 % predicted over short periods prohibits accurate estimation of an individual's *current* rate of lung function decline, with several years of data collection required to obtain reasonable estimates [12]. Unfortunately, an individual's *past* rate of decline is not predictive of immediate future decline. For instance, young patients that have lost little to no FEV_1 are at the greatest risk of immediate rapid decline [10]. Further, there is no opportunity to mitigate *past* FEV_1 decline through disease management. Longitudinal analyses have identified risk factors for future FEV_1 decline in various age groups that allow us to predict future disease aggressiveness. The ability to identify patients that may "appear" to be at low risk (primarily because they are at an early stage of lung disease) but are determined to actually be at high risk for decline allows clinicians to rationally consider the risks and benefits of interventions that may slow the rate of lung function decline. Recognition that producing a "sustained improvement" in lung function may not equate to a reduction in the rate of lung function decline has stimulated retrospective analyses of observational databases to determine which chronic CF pulmonary therapies may in fact be disease modifying. As these analyses are published, the ability to selectively and aggressively target higher risk individuals, regardless of their disease stage, has the potential to dramatically improve overall survival in CF.

Conflict of interest statement

Michael Konstan, MD and Jeffrey Wagener, MD are members of the scientific advisory group for the Epidemiologic Study of Cystic Fibrosis (ESCF), and have received honoraria from Genentech, Inc. for consulting activities associated with ESCF and other studies sponsored by Genentech. Drs. Konstan's and Wagener's institutions have received grant support from Genentech for their participation in ESCF and other studies sponsored by Genentech. Dr. Wagener was previously employed by Genentech, Inc. from 2005 to 2007, Donald VanDevanter, PhD is a paid consultant to Genentech, Inc.

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